



ENHANCED BIOAVAILABILITY OF DRUGS VIA INTRANASAL DRUG DELIVERY SYSTEM

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ABSTRACT

The aim of present investigation is to explain the enhancement of bioavailability of drug through intranasal drug delivery system. Intranasal Therapy has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. Recently, it has been shown that many drugs have better bioavailability by nasal route than the oral route. This has been attributed to rich vasculature and a highly permeable structure of the nasal mucosa coupled with avoidance of hepatic first-pass elimination, gut wall metabolism and/or destruction in the gastrointestinal tract. Intranasal microemulsion, gels, nanoparticles, liposome and microspheres have gained increased interest in recent years as a delivery system for protein and peptides through the nasal route. Thus this review focuses on nasal drug delivery, nasal drug absorption mechanisms, various mechanisms for increasing the bioavailability of drug, and their applications in drug delivery.

Key words: Nasal, bioavailability, mechanism and permeation enhancer.

INTRODUCTION

The nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption. This is due to the large surface area, porous endothelial membrane, high total blood flow, the avoidance of first-pass metabolism, and ready accessibility. The nasal administration of drugs, including numerous compounds, peptide and protein drugs, for systemic medication has been widely investigated in recent years. The administration of drugs via nose is not a novel approach for drug delivery. In ancient days, nasal drug delivery was used for the systemic administration of psychotherapeutic compounds and other similar substances. But in modern pharmaceuticals, nasal delivery is considered as route of choice for local effect rather than systemic effects. Delivery of drugs via nose for maintenance of therapy of nasal allergy, sinusitis, nasal congestion, and nasal infection of routine practice¹. Intranasal delivery does not require any modification of the therapeutic agents and does not require that drugs be coupled with any carrier like in case of drug delivery across the BBB. A wide variety of therapeutic agents, including both small molecules and macromolecules can be successfully delivered, including to the CNS, using this intranasal method². In spite of the advantages cited above, the nasal route of drug delivery is associated with several limitations such as risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the drug and from the excipients. The absorption enhancers used may disrupt and even dissolve the nasal membrane in high concentration. Also, the untoward immunogenic effects might arise with the route. The most important limitation is the mechanical loss of the dosage form into the other parts of the respiratory tract like lungs due to high mucociliary clearance which results in low bioavailability due to short residence time of the drug at the site of absorption³. The various formulations administered by the nasal route include the nasal powders, drops and spray. Apart from these, in order to increase the residence times of the drug in the nasal cavity, Bioadhesive formulations, microspheres and gels are used. The nasal route has received

the great attention as a route of vaccination⁴. Nasal delivery of suitable antigen along with proper adjuvant to the nasal associated lymphoid tissue (NALT) has potential to induce humoral and cell mediated immunity. Nasal route is the route of choice for rapid mass immunization in developing countries and disaster area⁵.

BARRIER TO NASAL DRUG DELIVERY

Intranasal drug delivery is considered as a lucrative route of drug delivery system for formulation scientist because of its easy and simple formulation strategies. A large number of factors influenced therapeutic efficacy as well as toxicity of nasal administered drug product⁶. A large number of factors serve as barrier for systemic bioavailability of nasal drug product, which have been described as follows⁷(fig.1.).

PHYSIOLOGICAL BARRIER

Blood flow

Rich supply of blood and a large surface area make the nasal mucosa an optimal location for drug absorption. Nasal absorption of drugs is influenced by blood flow rate, as it increases the amount of drug that passes through the membrane and hence reaching the general circulation. From above observations, it was concluded that vasoconstriction decreases nasal drug absorption by diminishing the blood flow⁸.

Mucociliary clearance

Nasal mucociliary clearance is the most important Physiological barrier, which reduces the nasal residential time of drugs and/or dosage forms. Bioavailability of nasal dosage forms depends on nasal residential time in the nasal cavity. The nasal mucociliary clearance transports the mucus layer that covers the nasal epithelium towards the nasopharynx by ciliary beating⁹. Nasal mucus layer defend the respiratory tract by preventing the lungs from foreign substances, pathogens and particles carried by inhaled air. These agents adhere to the mucus layer and transported to the gastrointestinal tract. Above elimination is designated MCC and it influences significantly the nasal drug absorption. The MCC system has been described as a “conveyer belt” wherein cilia provide the driving force whereas mucus acts as

a sticky fluid that collects and disposes foreign particles. Hence, Mucociliary clearance efficiency depends on the length, density and beat frequency of cilia as well as the amount and viscoelastic properties of mucus. MCC may be increased by all factors that increase mucus production, decrease mucus viscosity or increase ciliary beat frequency¹⁰. In physiological conditions, mucus is transported at a rate of 5 mm/min and its transit time in human nasal cavity is reported to be 15-20 min¹¹.

Enzymatic degradation

Intranasally administration of drugs avoids gastrointestinal and hepatic first-pass effect. Drugs may be metabolized in lumen of nasal cavity due to the presence of a broad range of metabolic enzymes in nasal tissues. Some examples of enzyme which may play role in enzymatic degradation of drugs are carboxyl esterase, aldehyde dehydrogenases, epoxide hydrolases, glutathione S-transferases and Cytochrome P450 isoenzymes have been found in nasal epithelial cells. The proteolytic enzymes (amino peptidases and proteases) were also found and they play an important role in degradation of calcitonin, insulin and desmopressin. The pharmacokinetic and pharmacodynamic profile of drugs administered through nasal route may be affected by xenobiotic metabolizing enzymes¹². In this context, although the nasal first-pass metabolism is usually weaker than hepatic and intestinal ones it cannot be ignored¹³.

Pathological condition

Intranasal pathologies may affect the nasal mucociliary transport process and/or capacity for nasal absorption (fig. 2 & 3).

PHYSIOCHEMICAL PROPERTIES OF DRUGS (Fig.4)

Chemical forms

The chemical form of a drug is important in determining absorption. For example, conversion of the drug into a salt or ester form can also alter its absorption¹⁴. Huang *et al* (1985) studied the effect of structural modification of drug on absorption. It was observed that in-situ nasal absorption of carboxylic acid esters of L-Tyrosine was significantly greater than that of L-Tyrosine¹⁵.

Polymorphism

Polymorphism is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological membranes¹⁴.

Molecular weight

A linear inverse correlation has been reported between the absorption of drugs and molecular weight up to 300 Da. Absorption decreases significantly if the molecular weight is greater than 1000 Da except with the use of absorption enhancers. Shape is also important. Linear molecules have lower absorption than cyclic – shaped molecules¹⁴.

Particle size

It has been reported that particle sizes greater than 10µm are deposited in the nasal cavity. Too fine particles, below 5 microns should be avoided for nasal administration as they are inhaled directly into the lungs¹⁶.

Solubility and dissolution rate

Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions¹⁶. The absorption profile is influenced not only by drug solubility but also by the nature of pharmaceutical preparations, which have to guarantee the delivery of drug at therapeutically relevant doses. Due to the small size of nasal

cavity, the allowable volume of drug solution is low for intranasal drug administration. Thereby, drugs poorly soluble in water and/or requiring high doses may constitute a problem¹⁷. The particles deposited in the nasal cavity need to be dissolved prior to absorption. If a drug remains as particles or is cleared away, no absorption occurs¹⁶.

FORMULATION FACTORS (Fig.5)

pH of the formulation

Both the pH of the nasal cavity and pKa of a particular drug need to be considered to optimize systemic absorption. Nasal irritation is minimized when products are delivered with pH, in the range of 4.5 to 6.5. Also, volume and concentration are important to consider. The delivery volume is limited by the size of the nasal cavity. An upper limit of 25 mg/dose and a volume of 25 to 200 µl/ nostril have been suggested:

- To avoid irritation of nasal mucosa,
- To allow the drug to be available in unionized form for absorption,
- To prevent growth of pathogenic bacteria in the nasal passage,
- To maintain functionality of excipients such as preservatives, and
- To sustain normal physiological ciliary movement¹⁶.

Buffer capacity

Nasal formulations are generally administered in small volumes ranging from 25 to 200µL. Hence, nasal secretions may alter the pH of the administered dose. This can affect the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ¹⁶.

Viscosity

A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs¹⁸.

Drug concentration, dose and dose volume

Drug concentration, dose and volume of administration are three interrelated parameters that impact the performance of the nasal delivery performance. Nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments¹⁶.

Role of absorption enhancers

Absorption enhancers may be required when a drug exhibits poor membrane permeability, large molecular size, lack of lipophilicity and enzymatic degradation by amino peptidases. Osmolarity and pH may accelerate the enhancing effect. Absorption enhancers improve absorption through many different mechanisms, such as increasing membrane fluidity, increasing nasal blood flow, decreasing mucus viscosity, and enzyme limitation¹⁶.

STRATEGIES TO IMPROVE THE BIOAVAILABILITY OF DRUGS

A large number of formulation strategies are made available to improve the nasal bioavailability of nasal dosage forms. The basic mechanisms for enhancement of bioavailability are as follows (i) formulation of mucoadhesive dosages for to improve the nasal residence time, (ii) usage of enzyme inhibitors to eliminate the nasal metabolism, (iii) incorporating nasal permeation enhancers to improve the absorption, (iv) prodrug approach for optimizing favourable

physicochemical properties, and (v) particulate drug delivery. Any one of the approach or combination of two or more strategies is widely used to improve the bioavailability of the nasal formulations. They are discussed one by one as follows.

ENZYMATIC INHIBITORS

Nasal mucus layer and nasal mucosa act as enzymatic barriers during nasal drug delivery, because they have a wide variety of enzymes. Particularly, enzyme inhibitors are essential components of formulation, while developing a dosage form for protein and peptide molecules. Mostly proteases and peptidases inhibitors are widely used to improve the bioavailability of protein and peptide molecules. For example, bestatine and comostate amylase are used as aminoptidases inhibitors and leupeptine and aprotinin as trypsin inhibitors probably involved in the degradation of calcitonin¹⁹. Furthermore, bacitracin, amastatin, boroleucin and puromycin¹⁹⁻²¹ have been used to avoid enzymatic degradation of drugs such as leucine enkephalin^{22, 23} and human growth hormone²⁴. Finally, enzymatic inhibition can also be achieved using certain absorption enhancers (bile salt and fusidic acid)²⁵. It is demonstrated that disodium ethylenediaminetetraacetate, an absorption enhancer, reduces enzymatic degradation of beta sheet breaker peptide used for the treatment of Alzheimer's disease²⁶.

NASAL PERMEATION ENHANCERS

Small and large hydrophilic drugs may be poorly permeable across nasal epithelium and may show an insufficient bioavailability. Complete mechanism of drug absorption enhancement through nasal mucosa is not known. However, various mechanisms such as increase in the membrane fluidity, creating transient hydrophilic pores, decreasing the viscosity of mucus layer and opening up of tight junctions are the proposed mechanism of permeation enhancers which improve the bioavailability of nasal dosage forms²⁷. Some of the permeation enhancers like bile salts and fusidic acid derivatives can also inhibit the enzymatic activity in the membrane, thereby improving bioavailability. Even though nasal permeation enhancers can improve the therapeutic efficacy of drug products, its toxicity should be considered while developing dosage form. One of the most common and frequently reported problems with permeation enhancers is the nasal irritation during administration of nasal dosage form²⁸. The ideal characteristic of nasal permeations is as follows.

- It should be pharmacologically inert.
- It should be non-allergic, non-toxic and non-irritating.
- It should be highly potent.
- It should be compatible with a wide variety of drugs and excipients.
- It should be odourless, colorless and tasteless.
- It should be inexpensive and readily available in highest purity.
- It should be accepted by many regulatory agencies all around the world.

The permeation enhancer not only can lead to improvement in absorption and bioavailability but also provide uniform dosing efficacy. Their non specific action, long term toxicity, and nasal irritation are the major hurdles, which affects the clinical applicability of permeation enhancers in the development of nasal dosage form.

Cyclodextrins act as solubilizer and permeation enhancer for nasal drug delivery and they are well tolerated in humans²⁹.

Amongst cyclodextrin, beta cyclodextrin is being considered to have Generally Recognised As Safe (GRAS) status. All other cyclodextrin are experimental material at this time. Schipper and coworkers studied the beta cyclodextrin as permeation enhancer for nasal drug delivery of insulin³⁰. The administration of insulin with 5% solution of dimethyl beta cyclodextrin did not enhance the absorption of insulin in rabbits, whereas powder dosage form significantly enhances the bioavailability of insulin in rabbits³⁰. Several compounds such as calcitonin, cartison, diazepam and naproxen investigated for their nasal bioavailability enhancement using cyclodextrin as the permeation enhancer. Surfactants are the most effective permeation enhancers but the issues like nasal irritation, epithelial toxicity, ciliostatic activity are the barriers for usage of surfactant as a nasal permeation enhancers. The extent of nasal absorption of insulin from nebulizer spray was observed to be pH dependent indicating maximum absorption at acidic pH. However, nasal absorption of insulin with surfactants like saponin, BL-9 and glycolate was significantly increased even at acidic pH, which correlated with hypoglycaemic activity. Comparative pharmacokinetics of intranasal delivery of salmon calcitonin was studied with various surfactants. A 10-fold increase serum calcitonin levels over control groups (calcitonin without surfactants) was observed in the formulations incorporated with surfactant. Laureth-9 was used as permeation enhancer to improve the bioavailability of insulin. the bile salts are believed to improve the bioavailability of both solubilisation of insulin and by direct effect of surfactant on the cell membrane³¹.

PRODRUG APPROACH

The term 'prodrug' was coined by Albert in 1951 and it is used to describe compounds that undergo biotransformation prior to exhibiting their pharmacological effect³². In recent days, designing of prodrug is used to improve the physicochemical properties such as solubility and compound lipophilicity to overcome the pharmacokinetics dimeritis associated with drug molecules. However, prodrug approach has also been used to reduce the presystemic metabolism and chemical decomposition. The basic principle associated with prodrug is to cover the undesired functional group (s) with other functional group, which usually are referred as promoity. Designing prodrug for improving the nasal bioavailability is one of the lucrative approaches specially for protein and peptide molecules. The ideal prodrug for bioavailability enhancement of protein and peptides would exhibit enhanced membrane permeability along with increased enzymatic stability. After crossing both enzymatic and membrane barrier, the prodrug undergoes enzymatic transformation to release the parent molecules³³.

An alternative approach to the use of prodrugs in order to increase drug solubility is the use of co-solvents³⁴. Co-solvents most used in intranasal formulations include glycerol, ethanol, propylene glycol and polyethylene glycol and may be of the most importance since they are nontoxic, pharmaceutically acceptable and non-irritant to nasal mucosa.

NASAL MUCOADHESIVE DRUG DELIVERY SYSTEM

MCC is one of the most important limiting factors for nasal drug delivery, because it reduces the time allowed for drug absorption. Thus, improving nasal drug absorption can also be achieved prolonging the contact time between drug and nasal mucosa. In this way, mucoadhesive drug delivery

systems have been developed³⁵⁻³⁷. Mucoadhesion implies the attachment of the drug delivery system to the mucus, involving an interaction between mucin and a synthetic or natural polymer called mucoadhesive. The sequential events that occur during this mucoadhesion include several steps. Firstly mucoadhesive systems absorb water from mucus layer and get wet and swelling. Following this, the polymer intimately penetrates into the mucus and, hence, localizes the formulation in nasal cavity, enhancing the drug concentration gradient across the epithelium³⁸.

Mucoadhesive drug delivery has been used to improve therapeutic efficacy of local as well as systemic drug delivery. The bioavailability of nasally administered drugs was improved with all kinds of therapeutic substances such as small organic molecules, antibiotics, vaccines, DNA, proteins and other macromolecules³⁹. The usage of PEG in nasal formulation should be carefully optimized, because it is irritant to nasal mucosa if concentration increases 10%. Mucoadhesive mostly used in intranasal drug delivery are chitosan, alginate and cellulose or its derivatives. Some of them may present other important characteristics which also enhance drug absorption. For example, chitosan is mucoadhesive and also causes a transient widening of epithelial tight junctions. Carbapol 934P and polycarbophil are mucoadhesive polymers that inhibit the trypsin proteolytic enzyme and, therefore, they can be used also to increase the stability of peptide drugs³⁸. Sodium alginate is a water-soluble, natural, linear polysaccharide which is widely used as a polymer matrix due to its non-toxicity, biocompatibility and gel formation stability. Indeed, it has the highest mucoadhesive strength compared with polymers such as polystyrene, chitosan, carboxymethylcellulose and poly (lactic acid).

Intranasal bioavailability aqueous solution of apomorphine was found to be 45%. The nasal bioavailability of apomorphine is rate limited by drainage of aqueous solution through nasopharynx and rapid oxidation in aqueous solution. Highest nasal bioavailability of 98% of apomorphine was achieved by using mucoadhesive polymer like carbopol, polyacrylic acid and Carboxymethylcellulose⁴⁰.

NOVEL DRUG FORMULATIONS

Several claims have been made in favour of developing nasal formulations containing liposomes, microspheres and nanoparticles for intranasal drug delivery. These systems can include, besides the drug, enzymatic inhibitors, nasal absorption enhancers or/and mucoadhesive polymers in order to improve the stability, membrane penetration and retention time in nasal cavity.

Liposomes

Liposomes are phospholipids vesicles composed by lipid bilayers enclosing one or more aqueous compartments and wherein drugs and other substances can be included. Liposomal drug delivery systems present various advantages such as the effective encapsulation of small and large molecules with a wide range of hydrophilicity and pKa values⁴¹.

Liposomes have been delivered by nasal route; the Amphiphilic nature of liposome is well characterized for favourable permeation of drugs through biological membranes⁴². The permeability of liposome entrapping insulin through nasal mucosa of rabbits has been studied with and without incorporating sodium glycolate as a permeation enhancer. The pharmacokinetics in rats showed high

permeability of liposomes penetrated with permeation enhancer than solution containing same quantity of permeation enhancer. The loading and leakage character of desmopressin loaded liposome and the effect of liposome on permeability of desmopressin on nasal mucosa was studied. High permeability of liposome was achieved than solution dosage form. In liposome formulation cationic liposomes are prone for higher permeability than negatively charged liposomes⁴².

Nanoparticles

Nanoparticles systems are being investigated to improve drug delivery and intranasal drug administration. Nanoparticles are solid colloidal particles with diameters ranging from 1-1000 nm⁴³. They consist of macromolecular materials and can be therapeutically used as adjuvant in vaccines or as drug carriers, in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached. Nanoparticles may offer several advantages due to their small size, but only the smallest nanoparticles penetrate the mucosal membrane by paracellular route and in a limited quantity because the tight junctions are in the order of 3.9-8.4 Å⁴³.

Microspheres

The microspheres used in nasal drug delivery are water insoluble but absorb water into sphere matrix, resulting in swelling of sphere and formation of the gel. The gel Formation improves the nasal residence time and hence improves the bioavailability. Another mechanism stated for improving nasal bioavailability is improving the nasal permeation by opening the tight junction of nasal epithelium. Microspheres are usually based on mucoadhesive polymers (chitosan, alginate), which present advantages for intranasal drug delivery. Furthermore, microspheres may also protect the drug from enzymatic metabolism and sustain drug release, prolonging its effect^{44, 45}. Wang et al. have investigated aminated gelatin microspheres as a nasal drug delivery system for insulin. They have observed a significant hypoglycemic effect when administered intranasally in dry powder form to rats, but no significant effect was achieved when given in a suspension.

Microemulsions

Intranasal microemulsion is one of the focused delivery options for noninvasive drug delivery to systemic circulation. Zhang et al (2004) studied the brain uptake of nimodipine by intranasal administration of nonionic surfactant based microemulsion and found three fold higher of nimodipine and higher ratios of AUC in brain tissues and cerebrospinal fluid to that in plasma⁴⁶. Vyas (2006) has reported that microemulsion formulations of clonazepam incorporated with mucoadhesive agents exhibited faster onset of action followed by prolonged duration of action in the treatment of status epilepticus⁴⁷. In other studies, Vyas *et al* reported rapid and larger extent of drug transport into rat brain following intranasal administration of mucoadhesive microemulsions of zolmitriptan and sumatriptan^{48, 49}. Mukesh *et al* (2008) studied the intranasal delivery of risperidone and concluded that significant quantity of risperidone was quickly and effectively delivered to the brain by intranasal administration of mucoadhesive nanoemulsion of risperidone⁵⁰.

DISCUSSION

The nasal mucosa offers several advantages for controlled drug delivery. The mucosa is well supplied with both vascular and lymphatic drainage; first-pass metabolism in the

liver and pre-systemic elimination in the GI tract is avoided. Nasal drug delivery has great potential to treat both chronic and acute disease. One of the most important factors hindering the quality of nasal product is inter and intra subject variability in pharmacokinetics of dosage form. Bioavailability of nasal drug product is one of the major challenges for pharmaceutical companies to bring their product in market. Nasal drug delivery is a promising area for systemic delivery of orally inefficient drugs as well as an attractive alternative for non-invasive delivery of potent peptide and perhaps protein drug molecules. The intranasal route is an accessible alternative to parenteral routes.

However, it was also stated that intranasal route presents several limitations which must be overcome to develop a successful nasal medicine. Physiological conditions, physicochemical properties of drugs and formulations are the most important factors determining nasal drug absorption. The use of prodrugs, enzymatic inhibitors, absorption enhancers, mucoadhesive drug delivery systems and new pharmaceutical formulations are, nowadays, among the mostly applied strategies. Nasal drug absorption mainly depends on the physiological conditions of the nose and also physicochemical properties of drugs. Much has been investigated and much more are to be investigated for the recent advancement of nasal drug delivery system.

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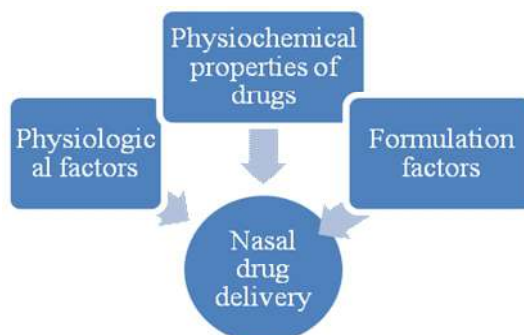


Fig.1: Factor affecting nasal absorption

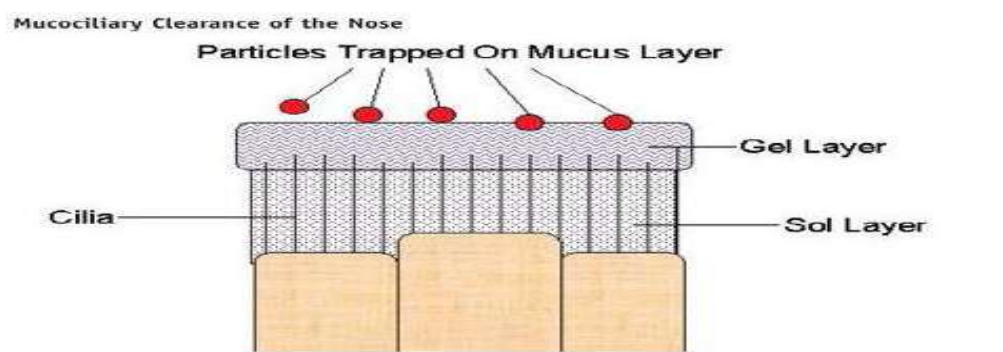


Fig. 2: Effect of mucociliary clearance on nasal drug absorption

Pathological conditions	Mucociliary clearance
Primary ciliary dysknesia Asthma	Impaired: absence or dyskinetic beating cilia Increased: inflammatory process and irritation Decreased: epithelial damage
Cystic fibrosis	Impaired: dehydration of mucus
Viral and bacterial infections	Compromised: change of mucus properties
Diabetes mellitus	Impaired: dehydration and microvascular damage

Fig. 3: Effect of pathological conditions on nasal mucociliary clearance.

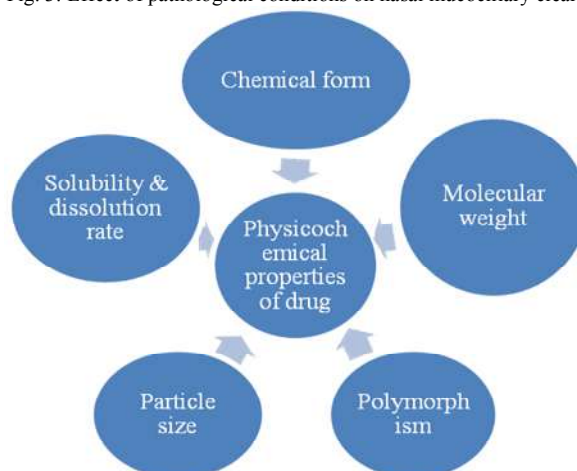


Fig.4: Drug related factors affecting nasal drug absorption.

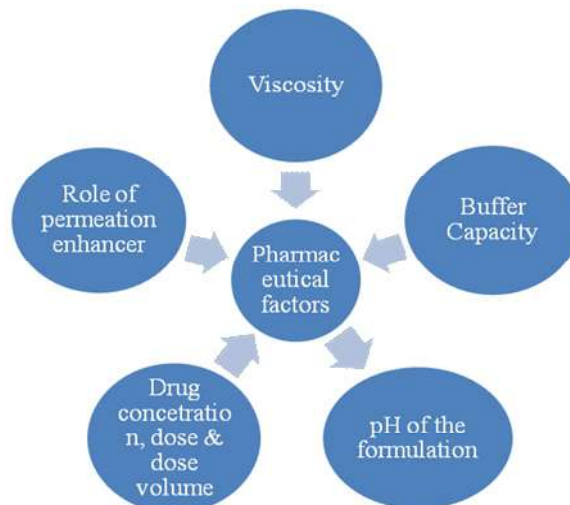


Fig.5: Drug related factors affecting nasal drug absorption.

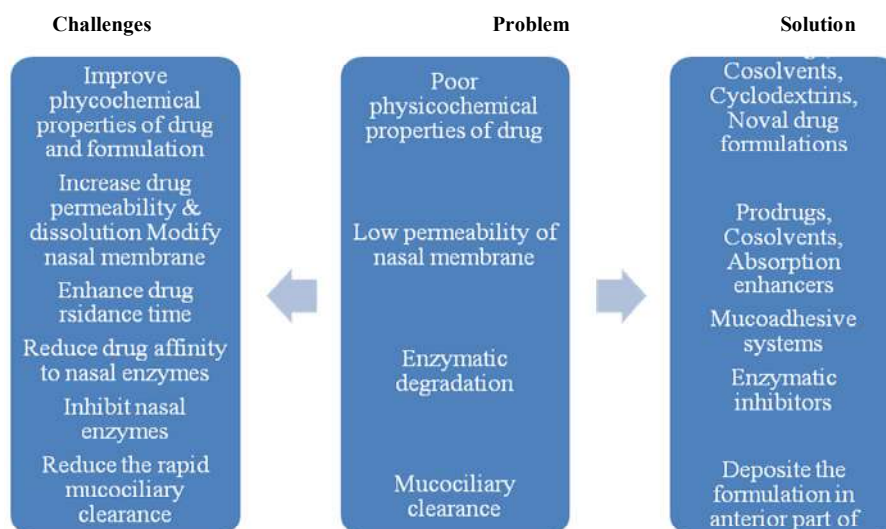


Fig.6: Nasal bioavailability-problems challenges and solutions.

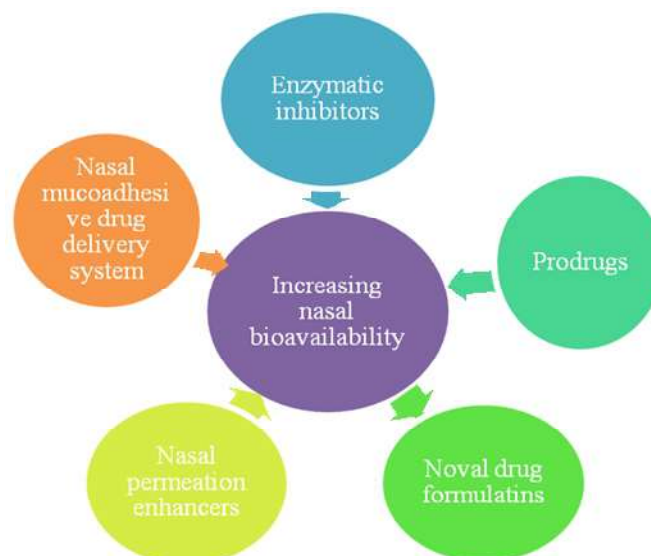


Fig.7: Method used for increasing nasal drug absorption